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Clinical Evaluation of Chemotherapy under Angiotensin II-Induced Hypertension in Patients with Advanced Cancer

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Summary

The clinical efficacy and indications for Angiotensin II (AT II)-induced hypertension chemotherapy were evaluated as a drug delivery system in 101 patients with advanced carcinoma. The sites of primary tumor studied included stomach (44), pancreas (18), colon (16), esophagus (6), bile duct (4), liver (3), breast (7) and 3 other single organs. Seventy four cases had distant metastases (lymph node (25), liver (29), peritoneum (16), and lung (4)). Additionally, the protocol was used 12 cases as postoperative adjuvant chemotherapy and 15 cases following exploratory laparotomy. The blood pressure was elevated to a level 1.5 times base-line. The regimens used consisted of MMC+ADR (55), FAM (38) and CDDP (8). The dosages administered were MMC 7 mg/m^2, ADR 14 mg/m^2 and 5-FU 350 mg/m^2. The cancer chemotherapy protocol with AT II was repeated for an average of 2.6 cycles with a 2–3 week interval.

The drug concentration in tumor tissues was increased 1.7 fold by AT II treatment. The response rate was 15.8% (CR 7 and PR 9), and in those patients with lymph node, liver and peritoneal metastases was 48.0, 6.9 and 6.3%, respectively. The serum levels of tumor markers decreased in 9 patients. Subjective symptoms, such as hoarseness, edema and pain, were improved. The mean survival in patients with distant metastasis who responded was 343 days, and in non-responders was only 168 days ($p<0.05$). The side effects of this therapy were slight, typically being grade 1 and 2.

Thus, the chemotherapeutic agents studied in conjunction with AT II were effective in patients with lymph node metastasis. Additionally, this regimen could be performed safely with minimal side effects.

Introduction

The delivery of anticancer drugs to tumor tissues is known to be one of the most important factors in determining the clinical efficacy of those chemotherapeutic agents. Angiotensin II (AT II)-in-

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duced hypertension has been used in association with cancer chemotherapy to increase delivery of the chemotherapeutic agents to the target tissues in cancer patients. Using this technique results in enhanced chemotherapeutic effects[10]. It was shown by analyzing the microhemodynamics of tumor vessels that the elevation in blood pressure induced by AT II results in a several-fold increase in tumor blood flow. This effect seems to be especially significant in the tumor vessels[13].

In this report, we evaluated the drug concentration in tumor tissues with AT II-induced hypertension and the clinical efficacy of this regimen including the incidence of side effects.

Materials and Methods

1. Patient profiles

From 1985 to 1989, 101 patients with advanced carcinoma received AT II-induced hypertension chemotherapy in Wakayama Medical College Hospital. This group included 6 with esophageal cancer, 44 with gastric cancer, 3 with hepatocellular carcinoma, 4 with bile duct carcinoma, 18 with pancreatic cancer, 16 with colon cancer, 7 with breast cancer and 3 other cancers. Distant metastases were present in 74 patients. Of these, 25 were to lymph nodes, 29 to the liver, 16 had peritoneal dissemination and 4 had lung metastasis. Exploratory laparotomy was initially performed in 15 patients who were then found to be inoperable. Twelve patients with Stage IV cancer received this regimen as a postoperative adjuvant chemotherapy. The male to female ratio was 67 : 34, and the mean age was 58 years old.

2. Preparation of AT II and clinical procedure

The AT II (CIBA-GEIGY, Basel, Switzerland) was dissolved in 500 ml of physiological saline at a concentration of 5 μg/ml. This was then given by continuous infusion using an infusion pump. Blood pressure was monitored to achieve a mean pressure 1.5 times baseline, but never over 150 mmHg. The anticancer agents were then given by intravenous bolus injection through the opposite arm from the AT II. The blood pressure was maintained at this elevated level for 10 minutes following administration of the chemotherapeutic agents.

3. Chemotherapeutic regimens

The combinations of mitomycin C (MMC) and adriamycin (ADR) were used in 55 cases, FAM (5-FU, ADR and MMC) in 38 cases, and cisplatin as a single agent was used in 8 patients. The respective doses of each drug were 7 mg/mm^2 for MMC, 14 mg/mm^2 for ADR, 350 mg/mm^2 for 5-FU and 60 mg/mm^2 for cisplatin. This schedule was repeated every 2–4 weeks. The average number of cycles was 2.6, with a range of one to seven cycles. The clinical efficacy was evaluated according to the Japanese Ministry of Public Welfare criteria.

4. Measurement of drug concentration in the tumor tissues

The intratumor concentration of cisplatin was measured in three patients with gastric carcinoma and Virchow lymph node metastases. The metastatic lymph nodes were resected at 10 minutes following administration of cisplatin (50 mg/body) with AT II-induced hypertension. The intratumor concentration of total platinum was then measured by atomic absorption spectrophotometry.

Results

1. Elevation of blood pressure by AT II

The blood pressure was elevated to the target level (1.46±0.15 fold) in all patients within 2–3 minutes using a flow rate of 20–35 ml/h of AT II. This level was reliably maintained unitil discontinuation of AT II. When AT II infusion was discontinued, the blood pressure returned to the previous level within a few minutes.

2. Increased concentration of chemotherapeutic agents in the tumor tissues

The intratumor concentration of cisplatin was measured in patients with gastric carcinoma and Virchow lymph node metastases. In patient 1, the intratumor concentration of cisplatin using AT II-induced hypertension was 2.23 μg/g. This represents a 1.7 fold increase over that obtained with normotension. In patients 2 and 3, the concentration of cisplatin using AT II-induced hypertension was 4.02 and 1.44 μg/g, respectively. The mean concentration of cisplatin in these three cases was 2.56±1.08 μg/g (Table 1).

3. Therapeutic effects in advanced cancer patients

Seven of 101 patients (6.9%) achieved a complete response (CR) and 9 patients (8.9%) achieved a partial response (PR). This gave a response rate of 15.8% (CR+PR). In 74 patients with distant metastasis, the response rate was 21.6% (CR 9.5%+PR 12.1%). The relationship between response rate and site of metastasis revealed that CR was obtained in 7 patients with lymph node metastasis and PR was obtained in 5, 2, 1 and 1 patients with lymph node, liver, peritoneal dissemination and lung metastases, respectively. In patients with lymph node metastases, the response rate was 48.0% which was significantly higher than those of the other metastatic lesions ($p<0.05$) (Table 2).

4. Clinical efficacy in patients with lymph node metastasis

Table 1 Concentration of cisplatin in metastatic lymph nodes

	Patient age, sex	Concentration in tumor tissues (μg/g)	
		Normotension	Induced hypertension
1	63, female	1.31	2.23
2	72, female	ND	4.02
3	67, female	ND	1.44
			Mean 2.56±1.08

The total platinum concentration in tumor tissue was measured. Virchow lymph nodes from three patients with gastric cancer were resected at 10 minutes following intravenous administration of 50 mg cisplatin.
ND; not determined.

Table 2 Response rate for cancer chemotherapy under ATII-induced hypertension.

Location of metastasis	Clinical response		Response rate
	CR	PR	
Lymph node (25 cases)	28% (7/25)	20% (5/25)	48% (12/25)*
Liver (29 cases)	0	6.9% (2/29)	6.9% (2/29)
Peritoneum (16 cases)	0	6.3% (1/16)	6.3% (1/16)
Lung (4 cases)	0	25% (1/4)	25% (1/4)
Overall response rate	9.5% (7/74)	12.1% (9/74)	21.6% (16/74)

* $p<0.05$, compared with response rates for other locations of metastases.

Seven patients achieved CR and 5 patients achieved PR of 25 patients with lymph node metastases. The locations of the metastatic lymph node in those patients who obtained CR included six with Virchow lymph nodes alone and one thyroid cancer patient with a left cervical lymph node

Table 3 Effects of ATII-induced hypertension chemotherapy against metastatic lymph nodes.
CR: 7 cases

Patient No.	Primary lesion	Metastasis	Size of lymph nodes		Response period (days)
			Before	After	
81	thyroid	Cervical	15×15	disappeared	360
20	stomach	Virchow	17×16	disappeared	130
11	stomach	Virchow	20×16	disappeared	80
42	stomach	Virchow	20×14	disappeared	56
18	pancreas	Virchow	22×15	disappeared	45
90	colon	Virchow	7×6	disapperaed	90
101	rectum	Virchow	10×5	disappeared	40
					Mean 114 days
					Median 80 days

Table 3 (Continued)
PR: 5 cases

Patient No.	Primary lesion	Metastasis	Size of lymph nodes		Percent reduction	Response period (days)
			Before	After		
38	stomach	hepatic hilum	45×10	22×6	71%	95
82	stomach	Virchow	30×20	12×8	84%	83
33	stomach	Virchow	13×12	8×8	59%	44
15	stomach	Virchow	32×20	5×5	98%	40
43	esophagus	Virchow	20×20	14×12	58%	30
					Average 74%	Mean 58 days
						Median 44 days

Table 4 Decrease in serum levels of tumor markers.

Patient No.	Primary lesion	Tumor marker	No. of cycles	Treatment		Evaluation
				Before	After	
42	stomach	CEA	7	230	80 ng/ml	CR
11	stomach	CEA	4	129	26	CR
43	esophagus	CEA	2	14	5	PR
32	stomach	CEA	7	20	8	NC
86	stomach	CEA	6	11	5	NC
62	stomach	CEA	7	7	2	NC
94	stomach	CA19–9	4	10510	1290 U/ml	NC
97	stomach	CA19–9	2	2028	850	NC
31	pancreas	CA19–9	2	931	220	NC

metastasis. The mean duration of CR was 114 days with a median of 80 days. PR was obtained in one gastric cancer patient with metastatic hepatic lymph nodes and 4 patients with Virchow lymph nodes. The degree of tumor regression ranged from 58% to 96%. The mean duration of PR was 58 days with a median of 44 days (Table 3).

5. Decrease in serum levels of tumor markers

Nine patients achieved a decrease in serum carcinoembryonic antigen (CEA) or CA19–9 level (6 and 3 patients, respectively). This included 7 patients with gastric cancer, 1 with esophageal cancer and 1 with pancreatic cancer. Two patients obtained CR and 1 patients obtained PR among patients noted to have a decrease in tumor markers (Table 4).

6. Improvement in subjective symptoms

Subjective symptoms were also improved with AT II-induced hypertension chemotherapy. Two patients with metastatic cervical lymph nodes had resolution of hoarseness (33%), 4 patients had resolution of upper and lower extremity edema (44%), and 3 patients had resolution of pain (33%) (Tabel 5).

7. Survival rate

Patients with evidence of tumor response had a mean survival of 343 ± 121 days and a medium survival of 312 days. However, non-responders survived a mean of only 168 ± 97 days. With a median of 157 days, amongst 74 patients with distant metastases. There was a significant difference between the survival period of responders and non-responders ($p < 0.05$) (Table 6).

8. Adverse effects of the treatment

The side effects accompaning the AT II-induced hypertension chemotherapy were few. These side effects accompaning with induced hypertension included headache (5.9%), retrosternal pressure (2.9%) and abdominal pain (2.0%). These side effects were reduced with a slight decrease in the rate of AT II-infusion. The side effects of the anticancer drugs included nausea, vomiting,

Table 5 Improvement in subjective symptoms following treatment.

Symptoma	Effective rate (%)
Hoarseness[1]	2/6 (33%)
Edema[2]	4/9 (44%)
Abdominal or back pain[3]	3/10 (30%)

1) Hoarseness was due to paralysis of the recurrent laryngeal nerve by tumor mass invasion.
2) Edema of the upper and lower extremities was due to disturbed lymphatic flow by metastatic lymph nodes.
3) Abdominal or back pain was due to metastatic lymph nodes in the paraaortic region.

Table 6 Survival time of responders and non-responders.
(74 cases with distant metastasis)

		Survival period	
		Mean (days)	Median (days)
Responders (CR+PR)	16 cases	343 ± 121*	312
Non-responders	58 cases	168 ± 97	157

* $P < 0.05$.

Table 7 Adverse effects of cancer chemotherapy.

1. Side effects due to induced hypertension.

Clinical symptoms	No. of case (%)
Headache	6 (5.9%)
Retrosternal pressure	3 (2.9%)
Abdominal pain	2 (2.0%)
	11/101 (109%)

2. Side effects due to anticancer drugs.

Clinical sings	No. of case (%)	Grade of side effects			
		1	2	3	4
Nausea/vomiting	22 (21.8%)	10	12	0	0
Myelosuppression	22 (21.8%)	11	9	1	1
Alopecia	4 (4.0%)	2	2	0	0
	48/101 (47.5%)	23	23	1	1

myelosuppression and alopecia. Nausea and vomiting occured in 22 patients (21.8%); grade 1 in 10 patients and grade 2 in 12 patients. Myelosuppression developed in 22 patients (21.8%) and 20 of these patients either grade 1 or 2. Only 2 patients suffered from severe leucocytopenia of grade 3 or 4, but the nadir was from 7 to 10 days. The leucocytopenia was reversible in all cases. Alopecia occured in 4.0% and therefore was not a frequent side effect (Table 7).

Disucussion

Accumulation of chemotherapeutic drug into tumor tissues is essential in cancer chemotherapy. The AT II-induced hypertension method has been adapted to cancer chemotherapy as a drug delivery system[10]. It has been found that tumor tissues, includeing metastatic lymph nodes, are composed of newly growing vessels which lack blood flow autoregulation and are influenced only secondarily by the responding somatic vessels[7]. It has been demonstrated that elevation of the mean arterial blood pressure to 150 mmHg by infusion of AT II selectively results in a 5–7 fold increase in blood flow in tumor tissues without increaseing blood flow in normal tissues[12]. ABE *et al.* reported that the intratumor concentration of fluorescein isothiocyanate-labeled neocarzinostatin using Donryu rats was approximately 2-fold higher in a group using AT II-induced hypertension compared to controls[2]. However, there have been no reports that clarify the enhancement in intratumor concentration of chemotherapeutic drugs in human cancer patients using AT II-induced hypertension.

In this study, we measured the intratumor concentration of chemotherapeutic drugs in cancer patients and showed that the concentration of chemotherapeutic drugs was elevated in tumor tissues by AT II-induced hypertension. The concentration in Virchow's lymph nodes following intravenous administration of 50 mg cisplatin under AT II-induced hypertension was 2.56 μg/g. This concentration was higher than serum Cmax obtained by intravenous administration of 100 mg cisplatin[5] and was proven to be an effective level for gastric cancer using in antitumor chemosensitivity test[14].

The combination chemotherapy of 5-FU, ADR and MMC (FAM therapy) has been reported as an effective regimen against advanced gastrointestinal cancer. The response rates for FAM therapy in early studies had been relatively good, that is, BITRAN *et al.* demonstrated that the response rate in pancreatic cancer was 40% and gastric cancer was 55%[4]. Other reports have achieved response rates ranging from 23% to 37%[6,11]. Since the criteria for response to cancer chemotherapy has recently become more strict, the response rates of FAM therapy are down to 7%–14% in advanced gastric or pancreatic cancer[3,9]. Although cisplatin has also been confirmed as an effective chemotherapeutic agent, the objective response rate remained at 22%[8] and 19% of patients with advanced gastric cancer[1].

WAKUI *et al.* demonstrated that the response rate of FAM therapy used in conjunction with AT II was 50% in gastric cancer[15]. In our study, the overall response rate was 21.6%. However, the response rate was 48% for patients with lymph node metastases and 34% (11 of 32 cases) in patients with gastric cancer and distant metastases. Thus, our method using AT II-induced hypertension was clinically beneficial compared with recent reports.

The side effects of AT II-induced hypertension chemotherapy were mild. OSTER *et al.* reported that 50% of patients on FAM therapy experienced severe or lifethreatening toxicity[9]. Another reported that 16% of patients suffered febrile leucopenia and one treatment-related death[3]. However, in the present study, the incidence of myelosuppression was 21.8% and almost all side effects were mild at grades 1 and 2.

AT II-induced hypertension chemotherapy is effective in cancer patients with metastatic lymph nodes and has mild side effects. Therefore, we proposed that the combination of AT II-induced hypertension with effective anticancer drugs may result in increased clinical efficacy.

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和文抄録

進行癌に対する Angiotensin II 昇圧抗癌化学療法の臨床評価

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進行癌101例を対象に，Angiotensin II (AT II) による昇圧で抗癌剤の腫瘍組織内への移行を亢進させる方法の癌化学療法における意義を検討した．抗癌剤はMMC, ADR, 5-FU またはCDDP を用い，2剤，または3剤同時併用で静注終了10分後まで昇圧状態を維持した．昇圧時の抗癌剤の組織内濃度は頸部リンパ節の生検結果より非昇圧時の1.7倍に増加することを確認した．有効率はCR 7例，PR 9例で，計16例（16%）に有効であり，再発形式別にみると，リンパ節転移48%，肝転移7%，腹膜転移7%に有効であった．自覚症状は嗄声，浮腫および疼痛の改善を認めた．腫瘍マーカーは9例で低下した．遠隔転移を有する74例の本法開始時からの生存期間は平均210日で，とくに有効例では343日と，無効例の168日より明らかに生存期間の延長効果を認めた ($p<0.05$)．副作用として軽度の消化器症状を22例，脱毛を4例に認め，22例に骨髄抑制がみられたが，いずれも Grade 1～2 であった．

以上より AT II 昇圧抗癌化学療法は副作用が少なく，ことにリンパ節転移を有する進行癌に対しては有効な治療法といえる．